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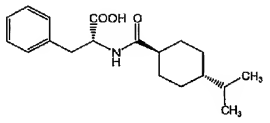

(I)

(57) Abstract: The present invention relates to an improved process for synthesizing highly pure nateglinide of formula-(I). More particularly, the present invention relates to the process for synthesizing highly enantiomerically pure nateglinide form B and form H directly from nateglinide alkyl ester.

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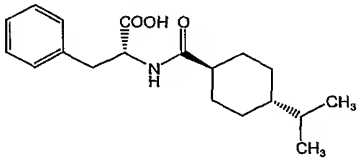
PROCESS FOR SYNTHESIZING HIGHLY PURE NATEGLINIDE POLYMORPHS

FIELD OF INVENTION

The present invention relates to an improved process for synthesizing highly pure nateglinide of formula-I.

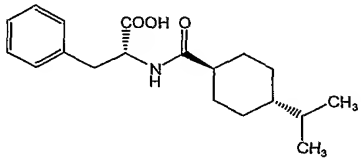


Formula I

More particularly, the present invention relates to the process for synthesizing highly enantiomerically pure nateglinide form B and form H directly from nateglinide alkyl ester.

BACKGROUND OF THE INVENTION

Nateglinide, of formula-I is marketed as starlix and is a useful therapeutic agent for the treatment of type II diabetes mellitus [also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes].



Formula I

Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas and is chemically known as *N*-(trans-4-isopropylcyclohexylcarbonyl)-*D*-phenyl alanine.

U.S. Patent 4,816,484 (referred herein as '484) and its subsequent reissue (U.S. Patent Re 34,878) disclosed hypoglycemic agents including nateglinide. Several methodologies have been disclosed for the preparation of hypoglycemic agents including nateglinide. In one of the methodologies, carboxylic acid is treated with *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide (DCC) to prepare the corresponding *N*-hydroxysuccinimide ester, which is further reacted with *D*-phenylalanine methyl ester hydrochloride to yield the corresponding *D*-phenylalanine methyl ester derivative which on subsequent base assisted hydrolysis followed by acidification with a dilute acid results in the formation of desired product. In the above patent the preparation of nateglinide from the corresponding trans-4-isopropylcyclohexane carboxylic acid is not exemplified using the above methodology. An example is given using cumic acid for the preparation of *N*-cumoyl-*D*-phenylalanine and it is

mentioned that following similar methodology, nateglinide can be prepared starting with trans-4-isopropylcyclohexane carboxylic acid in place of cumic acid.

As cumic acid is a planer compound and trans-4-isopropylcyclohexane carboxylic acid is a trans isomer so both are different in nature; therefore their corresponding *D*-phenylalanine derivatives can behave differently. Also the above patent fails to characterize the intermediates formed during the process of manufacture of nateglinide from trans-4-isopropylcyclohexane carboxylic acid. It has been observed that the given process and purification techniques used for the preparation of *N*-cumoyl-*D*-phenylalanine do not come off with the process for the preparation of nateglinide in high purity.

It is further disclosed that nateglinide can be recrystallized from methanol-water to give nateglinide in an overall yield of 65% starting from trans-4-isopropylcyclohexane carboxylic acid but purity is not mentioned.

We have found that following the methodology given in '484 patent during crystallization from water-methanol system as per the reported condition, nateglinide undergoes esterification to the form unacceptably higher levels of the nateglinide methyl ester as an impurity. Thus nateglinide is contaminated with the corresponding methyl ester, undesirable amounts of corresponding cis isomer as well as unacceptable levels of *L*-enantiomer that were usually above 0.15%. The enantiomeric purity being determined with the help of high performance liquid chromatography (HPLC) using chiral columns.

The aforesaid patent fails to mention the crystal nature and purity of nateglinide, although subsequent U.S. Patent no. 5,463,116 (referred herein as '116) discloses form H of nateglinide and refers to the crystalline form of nateglinide formed according to '484 as B-type crystals.

Further, it was observed that during scale up, the process described in '484 generates B-type crystals that are contaminated with polymorphic H-type crystals. Nateglinide is known to exist in a number of polymorphic forms, however in view of the regulatory and stability related issues, form B and form H of nateglinide are most sought after.

U.S. Patent application No. 2006/0148902 A1 describes a process for the direct conversion of nateglinide methyl ester into nateglinide form B by carrying out the hydrolysis in a mixture of water and toluene in the presence of a phase transfer catalyst and potassium hydroxide followed by addition of dilute hydrochloric acid, filtration, and drying to afford B-type crystals of nateglinide.

US Patent application 2003/0229249 A1 describes a process for the conversion of H-type crystals of nateglinide into B-type crystals from a mixture of water and ethanol and drying first at 40- 45°C till the moisture content has come down to 1% and finally crystal modification at

90°C under vacuum for 12 hours. The method again suffers from the disadvantage of formation of the nateglinide ethyl ester though free of H-type crystals.

US Patent application 2004/0181089 A1 discloses that the initially crystallized material formed by crystallization from methanol and water, as mentioned in '484, is isolated as a hydrate or a methanolate, which has been described as Z and E form respectively, that upon further drying gets converted into nateglinide form B.

Several alternate processes for generating nateglinide form B via crystallization of the nateglinide from different solvent systems have been reported, but there is hardly a process which would directly convert the nateglinide alkyl ester into pure nateglinide form B.

Similarly, several processes are disclosed in '116 for the generation of nateglinide form H by crystallizing nateglinide in a suitable solvent or solvent mixture such as acetone, ethanol and isopropanol with water. It is known that form H crystals of nateglinide prepared in accordance with the method described above, the synthesized crystals were small and it took a long time to complete the separation by filtration when the filtering device available on the industrial scale was used (US 7,208,622). Therefore, the above-described method is not practical for industrial purpose.

Numerous other processes for the preparation of stable form H are known in the art and are incorporated herein as reference.

US patent 7,208,622 describes a process in which trans 4-isopropylcyclohexane carbonyl chloride upon reaction with *D*-phenyl alanine in the presence of caustic solution followed by acidification in a mixture of water and acetone and crystallization at 58-72°C affords crystalline form H of nateglinide.

PCT Application WO 05/005373 discloses a process for the preparation of form H by treating nateglinide methyl ester in methanol with aqueous sodium hydroxide to yield the alkali salt and product is liberated with concentrated hydrochloric acid used in two lots.

Most of the prior art methods for the preparation of form H of nateglinide involve the use of alcoholic solvents. The major drawback of using alcoholic solvent during crystallization of nateglinide is that in the presence of alcohol, some of the nateglinide esterifies back to nateglinide alkyl ester, thus reducing the yield and purity of the product. Extensive purifications are required to obtain the purified product.

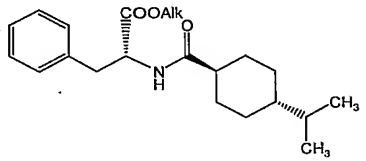
Above mentioned drawbacks urgently demand for new, improved and reliable processes of preparing pure nateglinide particularly in form B and form H, which are free from other forms as well as from nateglinide ester impurity that will be suitable for large-scale preparation in terms of simplicity, chemical yield, chemical as well as enantiomeric purity of the product.

The object of the present invention, thus, is to provide industrially advantageous processes for the preparation of pure nateglinide form B and form H, without allowing other forms to coexist, with low levels of *L*-nateglinide enantiomer and other impurities, and unique with respect to its simplicity, cost effectiveness, scalability.

Another object of the present invention is to provide an improved process for synthesizing highly pure nateglinide intermediates using novel purification techniques.

SUMMARY OF THE INVENTION

One aspect of the present invention relates to an improved process for the preparation of nateglinide form B, directly from *N*-(trans-4-isopropylcyclohexyl)carbonyl]-*D*-phenylalanine alkyl ester (nateglinide alkyl ester) of formula II,



Formula II

wherein Alk is C_1-C_4 alkyl

in the presence of a mixture of water and water miscible solvents and alkali metal hydroxide at 0-35°C, and at relatively dilute conditions followed by cooling the reaction mass to a temperature of 5 to 15°C, acidification with mineral acid such as hydrochloric acid in the presence of demineralized water and isolating highly pure nateglinide Form B.

Another aspect of the present invention relates to an improved process for preparing nateglinide polymorphic form B, comprising crystallizing any polymorphic form other than B-type crystals of nateglinide, from suitable solvents and isolating morphologically uniform nateglinide form B.

Yet another aspect of the present invention relates to an improved process for preparing nateglinide form B, comprising dissolving any polymorphic form of nateglinide, in a suitable solvent followed by the addition of anti-solvent and isolating morphologically uniform nateglinide form B.

Yet another aspect of the present invention relates to an improved process for the preparation of pure nateglinide form H, directly from nateglinide alkyl ester of formula II in the presence of base in a solution of suitable solvent like ethers and ketones and water and at relatively dilute conditions, followed by acidification with mineral acid such as hydrochloric acid in the presence of demineralized water and isolating nateglinide form H in high yield and purity.

Yet another aspect of the present invention relates to an improved process for preparing nateglinide in high yield and purity using novel purification processes for intermediates.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the powder X-ray diffraction pattern for nateglinide form B.

Figure 2 illustrates the differential scanning calorimetry for nateglinide form B.

Figure 3 illustrates the powder X-ray diffraction pattern for nateglinide form H.

Figure 4 illustrates the differential scanning calorimetry for nateglinide form H.

DETAILED DESCRIPTION OF THE INVENTION

More particularly, the present invention describes an improved process for the preparation of nateglinide polymorphs, particularly in form B and form H in high yield and purity.

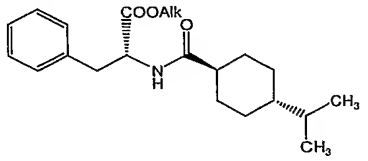
Nateglinide polymorphs, encompassed by the present invention may be characterized by at least one of X-Ray powder diffraction (XRD), FT-infrared spectroscopy (FTIR) or differential scanning calorimetry (DSC) techniques.

The XRD patterns of polymorphic form B and form H are measured on PANalytical X'Pert Pro diffractometer with Cu radiation and expressed in terms of two-theta, d-spacing and relative intensities.

DSC is conducted using standard conditions under N_2 gas flow at a temperature of 10°C/minute.

Specifically, the present invention describes an improved process for the preparation of nateglinide polymorphs, particularly in form B and form H in high yield and purity directly from nateglinide alkyl ester of formula II. Nateglinide alkyl ester of formula II can be prepared by the methods well known in art or as according to the processes of the present invention.

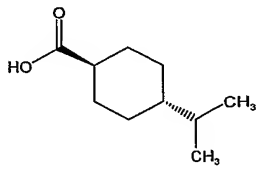
Yet another embodiment of the present invention provides a novel process for preparing pure *N*-(trans-4-isopropylcyclohexyl-1-carboxyl)-D-phenylalanine alkyl ester of formula II



Formula II

wherein Alk is C_1-C_4 alkyl

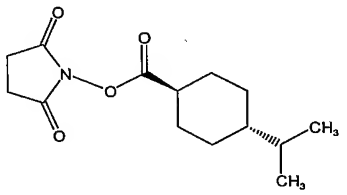
by initially stirring a suspension of trans-4-isopropylcyclohexyl-1-carboxylic acid of formula III,



Formula III

and *N*-hydroxysuccinimide in a suitable halogenated solvent preferably dichloromethane, at about ambient temperature, a suitable organic base is added and this mixture is stirred The

organic base can be selected from triethylamine, diisopropyl ethyl amine, triisopropyl amine, tributyl amine, pyridine or substituted pyridines, preferably triethylamine is used. The mixture is then cooled to a temperature of below 15°C and *N,N*-dicyclohexylcarbodiimide in dichloromethane is slowly added to the reaction mixture and the mixture is stirred at that temperature for few minutes to few hours preferably 30 minutes. The temperature is slowly raised to 30-50°C, preferably 38-40°C and the reaction mixture is stirred for 2-8 hours. Preferably the reaction mixture is stirred for 4-6 hours. The reaction completion is indicated by gas chromatographic analysis. The reaction mixture is cooled to ambient temperature followed by the addition of acetic acid and the reaction mixture is stirred for few minutes to few hours. Preferably the reaction mixture is stirred for 60-90 minutes. The reaction mass is further cooled to a temperature of below 15°C and precipitated dicyclohexyl urea, formed as a side product via the hydrolysis of *N,N*-dicyclohexylcarbodiimide, is removed by conventional procedures viz. filtration. The filtrate is successively washed with dilute hydrochloric acid, sodium bicarbonate solution and water, and the solvent is distilled off at 38-42°C and then completely removed under vacuum to give crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester of formula IV,



Formula IV

as a pale yellow solid having purity of 80-90% by gas chromatography (GC). The trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester of formula IV is characterized with the help of proton NMR, ^{13}C- NMR, FTIR and other spectroscopic methods.

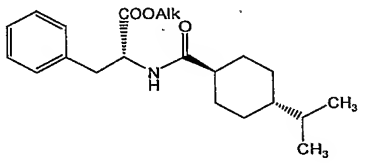
Trans-4-isopropylcyclohexyl-1-carboxylic acid of formula III used as starting material can be prepared by the methods known in prior art or can be procured from market.

According to yet another embodiment of the present invention, the crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester of formula IV can be purified from a suitable solvent selected from alcohols, esters, alkanes, ketones or mixture thereof. The alcohol can be selected from C_1-C_3 alcohols and alkane can be selected from C_5-C_7 alkane. The esters can be selected from esters formed by C_1-C_3 alcohols and C_1-C_3 acids. Ketones can be selected from acetone, diethyl ketone, methyl isobutyl ketone etc. Preferably, methanol, ethyl acetate, n-heptane, acetone or combination thereof can be used.

More particularly, crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester of formula IV is added to the suitable solvent and the mixture is heated with stirring at 50-75°C

for a period of 1-4 hours. Preferably, the reaction mass is heated at 60-65°C for about 1 hour. The mixture is slowly cooled to a temperature of below 15°C, stirred for few minutes to few hours. Preferably the reaction mixture is stirred for 60-90 minutes, filtered, slurry washed with solvent/ solvent mixture and dried to yield pure trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester of formula IV as a white to off white crystalline solid having purity greater than 96% by GC.

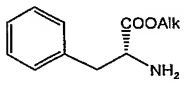
According to yet another embodiment of the present invention, trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester of formula IV can be converted to *N*-(trans-4-isopropylcyclohexyl-1-carboxyl)-*D*-phenylalanine alkyl ester of formula II



Formula II

wherein Alk is C_1-C_4 alkyl

Generally, a mixture of *N*-trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxy succinimide ester of formula IV and *D*-phenylalanine alkyl ester of formula V or salt thereof



Formula V

wherein Alk is C_1-C_4 alkyl

and a suitable base preferably triethylamine in halogenated solvent such as dichloromethane is heated at a temperature of 10-45°C with constant stirring over a period of 5-72 hours. Preferably, the reaction mixture is heated at a temperature of 10°C to reflux temperature for 5-60 hours. The quantity of the solvent used may vary depending upon the nature of the alkyl ester used and reaction conditions. Generally solvent is used from 3-50 times v/w and preferably 5-20 times v/w of the intermediate of formula IV. Progress of the reaction is monitored by gas chromatographic analysis. After the completion of the reaction, the reaction mixture is successively washed with dilute solution of hydrochloric acid, sodium bicarbonate solution and water at temperature below 25°C. The dichloromethane layer is dried over sodium sulfate, filtered and distilled at 38 - 40°C to afford crude nateglinide alkyl ester as off white to pale yellow solid.

D-Phenylalanine alkyl ester or salt thereof used in the above reaction can be procured from market or can be prepared by the methods known in prior art.

According to yet another embodiment of the present invention, nateglinide alkyl ester of formula II can be purified from a suitable solvent selected from alcohols, ketones, ethers or mixture thereof. The alcohol can be selected from C_1-C_3 alcohols, the ketones may be acetone, diethyl

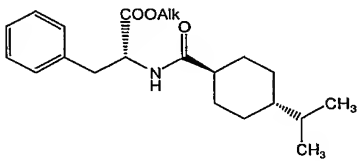
ketone, methyl isobutyl ketone, the ethers can be selected from tetrahydrofuran, 1,4-dimethoxy furan or alkyl ethers like diethyl ethers, diisopropyl ether, or a suitable mixture thereof.

Typically, the crude nateglinide alkyl ester of formula II (Alk is methyl) is dissolved in alcoholic or a ketonic solvent and the mixture is cooled to a temperature of below 10°C preferably at 5-8°C and is stirred for about an hour at the same temperature. The solid that precipitates out is filtered, washed with chilled alcohol or ketone and dried to afford pure nateglinide alkyl ester as a white to off white crystalline solid in high yield and purity greater than 98% by HPLC.

In an alternative process, nateglinide alkyl ester of formula II (Alk is methyl) is dissolved in a mixture of alcohol and an aliphatic alkane solvent. It is observed that purification can best be conducted in a mixture of n-heptane and methanol at ambient temperature and the mixture is slowly heated to 50-65°C with constant stirring for 1 hour at that temperature. The mixture is then cooled to a temperature of below 10°C, stirred for 1 hour, filtered, washed with same solvent mixture, and dried under vacuum to yield pure nateglinide methyl ester as a white to off white crystalline solid in high yield and purity greater than 98% by HPLC.

Nateglinide methyl ester of formula II can be converted to pharmaceutically pure nateglinide of formula I by conventional procedures known in the prior art or by the processes described in the present invention.

In one embodiment of the present invention, *N*-(trans-4-isopropylcyclohexyl-1-carboxyl)-*D*-phenylalanine alkyl ester (nateglinide alkyl ester) of formula II



Formula II

wherein Alk is C_1-C_4 alkyl

can directly be converted to pharmaceutically pure nateglinide form B. The alkyl ester is selected from C_1-C_4 alkyl which can be straight chain or branched chain and preferably ethyl and methyl esters are used. Typically, nateglinide alkyl ester of formula II (Alk is methyl) is added to a stirred solution of large volumes of demineralized water, a suitable solvent and alkali metal hydroxide preferably sodium hydroxide at 2-15°C, over a period of few minutes with constant stirring. Suitable solvent can preferably be selected from, but not limited to solvents like ether, alkyl alcohols, alkyl nitriles, formamides and the like or mixtures thereof. In the preferred embodiment, the solvents used are tetrahydrofuran, methanol, acetonitrile or mixtures thereof.

The reaction works with equal efficiency if aqueous sodium hydroxide solution is added to a suspension of nateglinide methyl ester in a mixture of water and organic solvent mentioned above. The amount of sodium hydroxide used varies between 1.1 to 3.0 molar equivalents, but

preferably 2.0-2.5 molar equivalents are used. The ratio of organic solvent and water used varies from 0.1:0.9 to 0.9:0.1, but is preferably from 0.3:0.7 to 0.4:0.6. Total quantity of solvents may vary depending upon the solvent and reaction condition and can be between 10 times to 200 times, preferably between 20 times to 100 times.

The temperature of the reaction mass is slowly raised to 25±5°C over a period of about a few minutes to a few hours, preferably for a period of about 1-2 hours. The reaction mass is further stirred for 6-12 hours at 25±5°C and progress of the reaction can be monitored by high performance liquid chromatography (HPLC) or thin layer chromatography (TLC). The solution is checked for clarity and the reaction mixture is cooled to 15-20°C, filtered to remove suspended particles and stirred for additional one hour at that temperature. The solution is further cooled to 5 to 15°C and the pH of the mixture is adjusted to 7.0 – 7.5 with dropwise addition of cooled hydrochloric acid. The mixture is further stirred for about an hour and then additional hydrochloric acid is added at 0-20°C, preferably at a temperature of 10-15°C to adjust the pH of the reaction mass to 1.5 – 2.5 with stirring for a period of about 60 minutes. The strength of the hydrochloric acid used may vary between 0.1 *N* to 6 *N*, preferably between 0.5 *N* to 3.5 *N*.

It is advantageous to carry out the acidification at below 20°C, more preferably below 15°C to avoid the formation of mixture of different polymorphic forms. The precipitated solid is quickly filtered under vacuum, washed successively with excess of water. It is first suck dried for a period of about 1-4 hours and then dried in oven at 40°C for about 10-15 hours till the moisture content is between 25-50%. Finally the precipitated solid is dried at 60-65°C under vacuum till the moisture content is below 0.5% to provide nateglinide in high yield and purity greater than 99.5% by HPLC. Alternatively, filtered material can be straightaway subjected to drying at 60-70°C under vacuum or under normal atmospheric conditions. The nateglinide thus isolated is of pharmaceutical grade in which no unidentified impurity is above 0.15% and displays physicochemical characteristics which corresponds to that of form B of nateglinide.

More importantly the invention results in the preparation of highly pure nateglinide form B without the contamination by any other polymorphic form, wherein the residual solvents levels are as per the ICH guidelines and which does not require any additional step of purification.

Another embodiment of the present invention encompasses methods for preparing nateglinide form B comprising dissolving nateglinide in a suitable solvent to form solution and then evaporating the solvent and collecting the precipitate.

More particularly H-type crystals of nateglinide or any other form or mixture thereof, is dissolved in a suitable solvent and filtered to remove suspended particles. The solvent used can be selected from, but not limited to ethers. In the preferred embodiment, the solvent used is

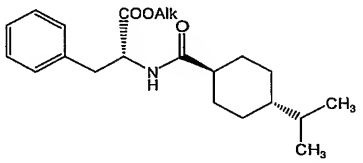
tetrahydrofuran, dimethyl ether, diethyl ether and the like. Nateglinide form B can then be isolated by conventional methods. However, other equivalent separation or isolation procedures could, of course, also be used.

Typically, the ether solvent, preferably tetrahydrofuran is evaporated under vacuum and the sample is dried under vacuum for 1-5 hours till the solvent has completely evaporated. The material is finally dried under vacuum at 60-70°C to afford nateglinide which displays characteristic patterns which correspond to that of nateglinide form B.

Another embodiment of the invention encompasses a method of preparing nateglinide form B comprising dissolving nateglinide in a solvent to form a mixture, cooling the mixture, adding an anti-solvent to precipitate nateglinide form B, and collecting the precipitate.

More particularly, nateglinide H-type crystals of nateglinide or any other form or mixture thereof is dissolved in a suitable solvent and the mixture is cooled to 3-20°C, preferably 5-10°C. Suitable solvent can preferably be selected from, but not limited to water miscible ethers, alcohols, nitriles or mixtures thereof. In the preferred embodiment, the solvent used is tetrahydrofuran, methanol or acetonitrile. This is followed by slow addition of anti-solvent to the solution and the mixture is stirred for 2 hours at 5-15°C. The anti-solvent is preferably water. Crystallization may occur spontaneously without any inducement. Another way of accelerating crystallization is by seeding with a crystal of nateglinide form B or scratching the inner surface of the crystallization vessel with a glass rod. The precipitated solid is isolated preferably by filtration, washed with excess of water, and dried at 60-70°C to afford nateglinide which displays characterization patterns which correspond to that of nateglinide form B.

In another embodiment of the present invention, *N*-(trans-4-isopropylcyclohexyl-1-carboxyl)-*D*-phenylalanine alkyl ester (nateglinide alkyl ester) of formula II



Formula II

wherein Alk is straight or branched chain C_1-C_4 alkyl,

can directly be converted to pharmaceutically pure nateglinide form H. The alkyl ester is selected from straight or branched chain C_1-C_4 alkyl and preferably ethyl and methyl esters are used. Typically, *N*-(trans-4-isopropylcyclohexyl-1-carboxyl)-*D*-phenylalanine alkyl ester of formula II (wherein Alk is preferably methyl) is suspended in a solution of demineralized water, a suitable solvent particularly ethers and ketones and treated with base at 2-15°C, over a period of few minutes with constant stirring. Suitable ethereal solvent can preferably be selected from, but not limited to solvents like tetrahydrofuran, 1,4-diethoxy tetrahydrofuran, 1,4-dimethoxy

tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, the like and mixtures thereof. Suitable ketonic solvent can preferably be selected from C_3-C_{10} ketones, more preferably aliphatic ketones like acetone, diethyl ketone, ethyl methyl ketone, diisopropyl ketone, methyl propyl ketone, methyl isobutyl ketone, the like and mixtures thereof can be employed. In the preferred embodiment, the solvent used is acetone or tetrahydrofuran. The base can be selected from alkali metal hydroxide, alkaline metal carbonate such as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, the like or a mixture thereof. Preferably potassium hydroxide and sodium hydroxide are used; most preferably sodium hydroxide is used.

The base can be added in pellet form, powdered form or as solution in water. The reaction works with equal efficiency if base is added to a suspension of nateglinide alkyl ester in a mixture of water and organic solvent mentioned above. In the present invention, the reaction is conducted preferably in the presence of large volumes of water. Moreover, whenever needed additional amount of water may be added any time during the course of reaction. The amount of base used varies between 1.05 to 5.0 molar equivalents, but preferably 1.15-3.5 molar equivalents are used. The ratio of solvent and water used varies from 0.05:0.9 to 0.9:0.1, but is preferably from 1.0:1.0 to 2.0:1.0. Total quantity of solvents may vary depending upon the solvent and reaction condition employed and can be between 5 times to 200 times, preferably between 10 times to 100 times. Both the solvent composition and the temperature of reaction mass during crystallization plays an important role in obtaining the desired polymorphic form and it has been found that use of dilute solution is ideal for non racemization of the resulting nateglinide.

The temperature of the reaction mass is slowly raised to 15-20°C over a period of about a few minutes to a few hours, preferably for a period of about 1-12 hours. Progress of the reaction can be monitored by high performance liquid chromatography or thin layer chromatography. The reaction solution is filtered if suspended particles are present. Depending upon the requirement, additional amount of water may be added to the reaction mixture after the completion of the reaction. Optionally small amount of organic solvent selected form acetonitrile, acetone, diethyl ketone, ethyl methyl ketone and the like can also be added. The pH of the mixture is then adjusted to 1.0 – 3.0 with addition of suitable mineral acid preferably hydrochloric acid with constant stirring at ambient temperature to precipitate nateglinide form H. The strength of the hydrochloric acid used may vary between 0.1 N to 12 N, preferably between 0.5 N to 3.5 N. The order and manner of combining hydrochloric acid and water at this stage are not crucial and may be varied. The hydrochloric acid and water may be added individually to the reaction mixture in any order or can be combined together as dilute solution. After complete addition of the acid, the reaction mass can be stirred at 5-60°C over a period of 1-24 hours, preferably for 4-15 hours. It is

advantageous to stir the reaction mass at 20-30°C if the solvent is ethereal solvent such as tetrahydrofuran, whereas in case of ketonic solvent, reaction mass can be stirred preferably at 10-20 °C to obtain pure form H.

The precipitated nateglinide form H is isolated using conventional methods like filtration and washed with excess of demineralized water. It is first suck dried for a period of about 1-10 hours and then dried in oven at 40-80°C for about 12-60 hours till the moisture content is below 0.5% to provide nateglinide in high yield and purity greater than 99.5%. Nateglinide thus isolated is of pharmaceutical grade in which no unidentified impurity is above 0.1% and displays physicochemical characteristics which corresponds to that of form H of nateglinide.

Major advantages realized in the present invention are:

1. The process leads to the formation of highly pure intermediates which upon hydrolysis lead to very high chemically and stereochemically pure nateglinide in high yield.
2. Formation of impurities like L-nateglinide or alkyl ester is minimized under the reaction conditions employed.
3. The process provides nateglinide polymorphic form B and H of very high chemical and stereochemical purity directly from nateglinide alkyl ester.
4. No purification or crystallization is required to prepare pure nateglinide polymorphic form B and H.

The present invention will now be illustrated by the following examples, which are not intended to limit the effective scope of the claims. Consequently, any variations of the invention described above are not to be regarded as departure from the spirit and scope of the invention as claimed.

EXAMPLES

Example 1: Preparation of trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxy succinimide ester

To a stirred suspension of trans-4-isopropylcyclohexyl-1-carboxylic acid (100 g) and *N*-hydroxysuccinimide (81.17 g, 1.2 molar eq) in dichloromethane (1200 ml), triethylamine (20.45 ml) was added at 25 to 30°C and the mixture was stirred till clear solution was obtained. The clear solution was cooled to 5-10°C and *N,N'*-dicyclohexylcarbodiimide (146.64 g) dissolved in dichloromethane (300 ml) was slowly added to the reaction mixture and the mixture was stirred at same temperature for 30 minutes. The temperature was slowly raised to 38- 40°C and stirred for 4-6 hours till the reaction was complete. The mixture was then cooled to 25-30°C and acetic acid (130 ml) was added to the reaction mixture and stirred for 60-90 minutes. The reaction mass was further cooled to 10-15°C and the precipitated dicyclohexyl urea was filtered off. The

dichloromethane filtrate was successively washed with aqueous sodium bicarbonate solution (1 x2.5 L), 1N hydrochloric acid (1 x1 L) and demineralized water (3 x 1.0 L) and dried over sodium sulfate. Dichloromethane was distilled off at 38-40°C and then completely removed under vacuum to give 154.0 g of the title compound as a pale yellow solid having purity 86.66% by gas chromatography.

Example 2: Purification of crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxy succinimide ester

Method 1: To the crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester (154 g), n-heptane (540 ml) and methanol (160 ml) were added and the mixture was heated with stirring to 60-65°C for 1 hour. The mixture was slowly cooled to 5-10°C, stirred for 60-90 minutes, filtered, slurry washed with a cooled mixture of n-heptane and methanol (9:1; 200 ml) and dried under vacuum at 50°C for 10-12 hours to yield 146g of title compound as a white to off white crystalline solid having purity of 96.7% by gas chromatography.

Method 2: To the crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester (154 g), ethyl acetate (1.0 L) was added and the mixture was heated with stirring to 60-65°C for 1 hour. The mixture was slowly cooled to 5-10°C, stirred for 60-90 minutes, filtered through hyflo bed to remove the suspended particles and the filtrate was evaporated under vacuum at 45-50°C. The residue thus obtained was further dried under vacuum at 50°C till most of ethyl acetate had been removed. n-Heptane was then added to the residue and the after stirring for 1 hour at 45-50°C, the product was filtered and dried under vacuum at 45-50°C for 10-12 hours to yield 139.55 g of title compound as a off white to pale yellow crystalline solid having purity of 96.2% by gas chromatography.

Method 3: Crude trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester (154 g) was dissolved in methanol (600 ml) at 55-60°C and the mixture was cooled to 5-8°C and stirred for 1 hour. The crystallized solid was then filtered under vacuum, slurry washed with chilled methanol (2 x100 ml) and dried under vacuum at 50°C for 10-12 hours to yield 130.0 g of title compound as a white to off white crystalline solid having purity of 97.84% by gas chromatography.

Example 3: Preparation of *N*-(trans-4-isopropylcyclohexyl-1-carbonyl)-D-phenylalanine methyl ester (Nateglinide methyl ester)

Method 1: A mixture of trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester (70g), *D*-phenylalanine methyl ester hydrochloride (63g, 1.1 mol eq.) and triethylamine (127.6 ml, 3.5 mol eq.) in dichloromethane (1400ml) was heated 38-40°C with continuous stirring over a period of 40-48 hours and progress of the reaction was monitored by gas chromatography.

After the reaction was over, the mixture was cooled to 15-20°C and successively washed with 1N hydrochloric acid(3 x 400 ml), sodium bicarbonate solution (3 x400 ml) and water (3 x 400ml). The dichloromethane was dried over sodium sulfate, filtered and distilled at 38-40°C to afford 85.5 g of the title compound as a pale yellow solid.

Method 2: A mixture of trans-4-isopropylcyclohexyl-1-carboxylate-*N*-hydroxysuccinimide ester (100g), *D*-phenylalanine methyl ester hydrochloride (88.78g, 1.1mol eq.) and triethylamine (182.4 ml, 3.5 mol eq.) in dichloromethane (500 ml) was stirred at 15-20°C for 20-24 hours and progress of the reaction was monitored by gas chromatography. After the reaction was over, the mixture was washed with 1N hydrochloric acid (3 x 500 ml), sodium bicarbonate solution (3 x500 ml) and water (3 x 500 ml). The dichloromethane was dried over sodium sulfate, filtered and distilled at 38-40°C to afford 110 g of the title compound as a pale yellow solid.

Example 4: Purification of crude nateglinide methyl ester

Method 1: Crude nateglinide methyl ester (85.5g) was dissolved in methanol (550 ml) and the mixture was cooled to 5-8°C and stirred for 1 hour. The precipitated solid was filtered, slurry washed with chilled methanol (5°C, 2 x 70 ml) and dried under vacuum at 45 -50°C for 5-8 hours to afford 63.35 g of pure title compound as a white to off white crystalline solid having purity of 98.8 % by HPLC.

Method 2: Crude nateglinide methyl ester (85.0 g) was added to n-heptane (448 ml) and methanol (112 ml) at 25-30°C and the mixture was slowly heated to 55-60°C and stirred for 1 hour. The mixture was then cooled to 5-10°C, stirred for 1 hour, filtered, slurry washed with a mixture of chilled n-heptane and methanol solution (4:1, 70 ml), and dried under vacuum at 45-50°C for 10-12 hours to yield 68. 5 g of pure title compound as a white to off white crystalline solid having purity of 98.18% by HPLC.

Method 3: Crude nateglinide methyl ester obtained above was dissolved in acetone (680 ml) at 50-55°C and stirred further and the mixture was cooled to 5-8°C (maintained for 1 hour) and stirred for 1 hour at that temperature. The precipitated solid was filtered, slurry washed with chilled acetone (5°C, 70 ml) and dried under vacuum at 45-50°C for 5-8 hours to afford 62.22 g of title compound as a white to off white crystalline solid having purity of 98.25% by HPLC.

Example 5: Preparation of pure nateglinide form B

Method 1: To a stirred solution of demineralized water (2400 ml), methanol (2400 ml) and sodium hydroxide (18.12 g, 2.5 mol eq.) at 5-8°C, pure nateglinide methyl ester (60.0 g) was added over a period of 3- 5 minutes and stirred for 15 minutes, the temperature was slowly raised to 26±2°C over a period of 60-90 minutes. The reaction mass was stirred for 8 hours at 26±2°C and progress of the reaction was monitored by high performance liquid chromatography. During

this time the reaction mass became clear. The reaction mixture was cooled to 10-15°C, filtered to remove suspended particles and stirred for additional one hour at that temperature and pH of the mixture was adjusted to 7.0 – 7.5 with drop wise addition of cooled 1N hydrochloric acid (10-15°C). The mixture was stirred for 1 hour at pH 7.0 – 7.5 and then additional 1 N hydrochloric acid was added at 10-15°C to adjust the pH to 1.5 – 2.5 and stirred for 30 minutes. The precipitated solid was quickly filtered under vacuum, successively slurry washed with cooled (10-15°C) mixture of methanol and demineralized water (50:50, 2 x 600 ml) and demineralized water (6 x 600 ml). The filtered material was first suck dried for 2 hours and then at dried in oven at 40 - 45°C for 12 hours (till the moisture content was between 11-50%) and then finally dried at 60-65°C under vacuum (till the moisture content was below 0.5%) to yield 48.3 g of nateglinide form B having purity 99.95% by HPLC.

Method 2: To a stirred solution of purified water (1500 ml), tetrahydrofuran (400 ml) and sodium hydroxide (0.45 mol, 18.12 g, 1.5 m.eq.) at 5-10°C, pure powdered nateglinide methyl ester (100 g, 0.30 moles) was added over a period of 3- 5 minutes. The temperature was slowly raised to 20–22°C and reaction mass was stirred at 20–22°C for 8-10 hours when the high performance liquid chromatography indicated the reaction to be complete. The reaction mass was filtered, further cooled to 5-8°C and pH was adjusted to 7.0–7.5 with drop wise addition of cooled (10-15°C) 1 N hydrochloric acid. The mixture was stirred for 1 hour at pH 7.0–7.5 and then additional 1 N hydrochloric acid was added at 5-8°C to adjust the pH to 1.5 – 2.5 and stirred for 60 minutes. The precipitated solid was filtered under vacuum, successively slurry washed with cooled purified water (3 x 500 ml), suck dried for 2 hours and then dried in oven at 40-45°C for 12 hours till the m/c between 11-50%. The product was then finally dried at 60-65°C under vacuum till the moisture content was below 0.5% to afford 91.0 g of nateglinide form B as a white crystalline solid having purity of 99.85% by HPLC.

Method 3: To a stirred solution of purified water (50 ml), tetrahydrofuran (12.5 ml), acetonitrile (12.5 ml) and sodium hydroxide (0.9 g, 0.225 M.) at 5-10°C, pure powdered nateglinide methyl ester (5.0 g, 0.015 moles) was added and after stirring for 15- 20 minutes at 5-10°C the temperature was slowly raised to 20–22°C and reaction mixture was stirred at 20–22°C for 8-10 hours when the thin layer chromatography indicated the reaction to be complete. The reaction mass was filtered, further cooled to 5-8°C and pH was adjusted to 1.5 to 2.5 with drop wise addition of cooled (10-15°C)1N hydrochloric acid and the reaction mixture was stirred for 60 minutes. The precipitated solid was filtered under vacuum, successively slurry washed with cooled purified water (5 x 50 ml), suck dried for 2 hours and then dried in oven at 40°C for 12 hours till the m/c between 11-50%). The product was then finally dried at 60-65°C under vacuum

till the moisture content was below 0.5% to afford 4.5 g of nateglinide form B as a white crystalline solid. (Yield 94.73 %) having purity of 99.85% by HPLC.

Example 6: Conversion of nateglinide to pure Nateglinide form B

Method 1: Nateglinide (100.0 g) was dissolved in tetrahydrofuran (250 ml) and the mixture was cooled to 5-8°C. Methanol (250 ml) was added and the mixture was stirred at 5-8°C for 5 minutes. Water (2000 ml was slowly added to the solution and the mixture was stirred for 2 hours at 5-10°C. The precipitated solid was filtered, washed with water (3 x1000 ml) and dried at 60 -70°C to afford nateglinide form B.

Method 2: Nateglinide (5.0 g) was dissolved in tetrahydrofuran (25 ml) and filtered to remove suspended particles. Tetrahydrofuran was then evaporated under vacuum and the sample was dried under vacuum for 2- 3 hours till the solvent had completely evaporated. The material was scrapped from the walls of the flask and finally dried under vacuum at 60 -70°C to afford 4.8 g of B-type crystals of nateglinide.

Method 3: Nateglinide (5.0 g, polymorphic form H) was dissolved in tetrahydrofuran (25 ml) and filtered to remove suspended particles. Tetrahydrofuran was then evaporated under vacuum and the sample was dried under vacuum for 2- 3 hours till the solvent had completely evaporated. n-Heptane was added to the flask and after stirring for 30 minutes, the powder was filtered, washed with n-heptane, and dried under vacuum at 60-70°C to afford 4.75 g of nateglinide form B.

Method 4: Nateglinide (100.0 g, polymorphic form H) was dissolved in tetrahydrofuran (500 ml) and the mixture was cooled to 5-8°C. Water (2000 ml) was slowly added to the solution and the mixture was stirred for 2 hours at 5-10°C. The precipitated solid was filtered, washed with water, and dried at 60-70°C to afford B-type crystals of nateglinide.

Method 5: Nateglinide (5.0 g, polymorphic form H) was dissolved in tetrahydrofuran (12.5 ml) at 25-35°C and acetonitrile (12.5 ml) was added and mixture was filtered to remove the suspended particles. After stirring for 5 minutes the mixture was cooled to 5-10 °C and purified water 100 ml) was slowly added to the reaction mixture. After stirring for 1 hour at that temperature, the precipitated solid was filtered and washed with cold water (5 x 50 ml), dried at 60-70°C under vacuum for 24 hours to afford 4.79 g of nateglinide form B as a white crystalline solid.

Example 7: Preparation of Nateglinide form H

Method 1: To a solution of sodium hydroxide (18.12 g, 1.5 moles) in demineralized water (1500 ml) and tetrahydrofuran (400 ml) at 5 to 10°C, nateglinide methyl ester (100 g, 0.30 moles) was added. The temperature was slowly raised to 20-22°C and reaction mass was stirred at 20-22°C

for 8-10 hours and progress of the reaction was monitored by high performance liquid chromatography. After completion of the reaction, the mixture was filtered to remove suspended particles. To the filtrate, demineralized water (1000 ml) was added and pH was adjusted to 1.5 – 2.5 with 1*N* hydrochloric acid. The reaction mass was stirred for 8 hours at 25-30°C, the solid, thus precipitated, was filtered and slurry washed with demineralized water (5 x 500 ml). The filtered material was suck dried for 2 hours and then dried at 45-60°C under vacuum (till the moisture content was below 0.5%) to afford 92.55 g of nateglinide form H having purity of 99.88 % by HPLC. Yield = 96.70 %

Method 2: To a solution of sodium hydroxide (18.12 g, 1.5 moles) in demineralized water (1500 ml) and tetrahydrofuran (400 ml) at 5 to 10°C, nateglinide methyl ester (100 g, 0.30 moles) was added. The temperature was slowly raised to 20-22°C and reaction mass was stirred at 20-22°C for 8-10 hours and progress of the reaction was monitored by HPLC. After completion of the reaction, the mixture was filtered to remove suspended particles and pH was adjusted to pH to 1.5 – 2.5 with 1N hydrochloric acid at 25-30°C. Demineralized water (1000 ml) was added to the reaction mixture and reaction mass was further stirred for 8 hours at 25-30°C. The precipitated solid was filtered and slurry washed with demineralized water (5 x 500 ml). The filtered material was suck dried for 2 hours and then dried at 45-60°C under vacuum (till the moisture content was below 0.5%) to afford 91.10 g of nateglinide form H having purity of 99.85 % by HPLC.Yield = 95.19 %

Method 3: To a solution of sodium hydroxide (18.12 g, 1.5 moles) in demineralized water (1500 ml) and tetrahydrofuran (400 ml) at 5 to 10°C, nateglinide methyl ester (100 g, 0.30 moles) was added. The temperature was slowly raised to 20-22°C and reaction mass was stirred at 20-22°C for 8-10 hours and progress of the reaction was monitored by HPLC. After completion of the reaction, the mixture was filtered to remove suspended particles and pH was adjusted to pH to 1.5 – 2.5 with 0.25 N hydrochloric acid and reaction mass was stirred for 8 hours at 25-30°C . The precipitated solid was filtered and slurry washed with demineralized water (5 x 500 ml). The filtered material was suck dried for 2 hours and then dried at 45-60°C under vacuum (till the moisture content was below 0.5%) to afford 86.10 g of nateglinide form H having purity of 99.91 % by HPLC. Yield = 89.80 %

Method 4:o a solution of sodium hydroxide (0.54 g) in demineralized water (45 ml) and tetrahydrofuran (12 ml) at 5-10°C, nateglinide methyl ester (3.0 g) was added. After stirring the reaction mass for 15- 20 minutes at 5-10°C, the temperature was slowly raised to 20-22°C and reaction mixture was further stirred at 20-22°C for 8-10 hours. Progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, acetonitrile (7.5 ml)

was added to the reaction mixture and the solution was filtered to remove suspended particles. pH of the reaction mass was adjusted to 1.5 to 2.5 with 1N hydrochloric acid. Demineralized water (30 ml) was added to the reaction mixture and the mixture was stirred for 8 hours at 25-30°C minutes. The precipitated solid was filtered and slurry washed with demineralized water (5 x 50 ml). The filtered material was suck dried for 2 hours and dried at 45 -60°C under vacuum (till the moisture content was below 0.5%) to afford 2.0 g of nateglinide form H.

Method 5: To a solution of sodium hydroxide (4.53 g, 0.11 moles) in demineralized water (625 ml) and tetrahydrofuran (125ml) at 5-10°C, nateglinide methyl ester (25 g, 0.075 mol) was added. The temperature was slowly raised to 20-22°C and reaction mass was stirred at 20-22°C for 8 hours and progress of the reaction was monitored by HPLC. After completion of the reaction, the mixture was filtered to remove suspended particles and pH was adjusted to 1.5 – 2.5 with 1N hydrochloric acid. The reaction mass was stirred for 8 hours at 25-30°C. The precipitated solid was filtered under vacuum, slurry washed with demineralized water (5 x 100 ml), suck dried for 2 hours and then dried at 45-60°C under vacuum (till moisture content was below 0.5%) to afford 22.88 g of nateglinide form H having purity of 99.78 % by HPLC. Yield = 95.57 %

Method 6: To a solution of sodium hydroxide (4.53 g, 0.11 moles) in demineralized water (875 ml) and tetrahydrofuran (125 ml) at 5-10°C, nateglinide methyl ester (25 g, 0.075 mol) was added. The temperature was slowly raised to 20-22°C and reaction mass was stirred at 20-22°C for 8-10 hours and progress of the reaction was monitored by HPLC. After completion of the reaction, the mixture was filtered to remove suspended particles and pH was adjusted to 1.5 – 2.5 with slow addition of 1N hydrochloric acid. The reaction mass was stirred for 8 hours at 25-30°C, the precipitated solid was filtered under vacuum, slurry washed with demineralized water (5 x 100 ml). The filtered mass was suck dried for 2 hours and then dried at 45-60°C under vacuum (till the moisture content was below 0.5%) to afford 23.21 g of nateglinide form H having purity of 99.85 % by HPLC. Yield = 96.82 %.

Method 7: Nateglinide methyl ester (80.0 g) was added to a solution of sodium hydroxide (14.50 g) in demineralized water (800 ml) and acetone (800 ml) at 5 to 10°C. The temperature was slowly raised to 15-20°C and reaction mass was stirred at 15-20°C for 4 hours when the HPLC indicated the reaction to be complete. The reaction mixture was filtered, pH was adjusted to 1.5 – 2.5 with slow addition of 1N hydrochloric acid and the reaction mass was stirred for 10 hours at 15-20°C. The precipitated solid was filtered under vacuum, successively slurry washed with demineralized water (5 x 400 ml), suck dried for 1 hour and then dried at 45-50°C under vacuum

till the moisture content was below 0.5% to afford 70.63 g of nateglinide as a white crystalline solid having purity 99.73 % by HPLC (Yield = 92.93 %)

Method 8: Nateglinide methyl ester (8.0 g) was added to a solution of sodium hydroxide (1.450 g) in demineralized water (40 ml) and acetone (80 ml) at 5 to 10°C. The temperature was slowly raised to 15-20°C and the reaction mass was stirred at 15-20°C for 4 hours when the HPLC indicated the reaction to be complete. The mixture was filtered and pH was adjusted to 1.5 – 2.5 with slow addition of 1N hydrochloric acid. Additional water (40 ml) was added to the reaction mixture and the reaction mass was stirred for 10 hours at 15-20°C. The precipitated solid was filtered under vacuum, successively slurry washed with demineralized water (5 x 400 ml), suck dried for 1 hour and then dried at 45-50°C under vacuum till the moisture content was below 0.5% to afford 7.23 g of nateglinide as a white crystalline solid having purity 99.89% by HPLC (Yield: 95.13 %).

Method 9: Nateglinide methyl ester (8.0 g, 0.024 moles) was added slowly to a solution of sodium hydroxide (14.50 g, 0.036 moles) in demineralized water (40.0 ml) and acetone (80 ml) at 5 to 10°C. The temperature was slowly raised to 15-20°C and the reaction mass was stirred at 15-20°C for 4 hours when the HPLC indicated the reaction to be complete. The mixture was filtered and the pH was adjusted to 1.5 – 2.5 with slow addition of 1N hydrochloric acid. The reaction mass was stirred for 10 hours at 15-20°C. The precipitated solid was filtered under vacuum, successively slurry washed with demineralized water (5 x 40 ml), suck dried for 1 hour and then dried at 45-50°C under vacuum till the moisture content was below 0.5% to afford 7.08 g of nateglinide as a white crystalline solid having purity 99.83% by HPLC (Yield = 93.15 %).

Method 10: Nateglinide methyl ester (10.0 g, 0.03 moles) was added to a solution of sodium hydroxide (1.81 g, 0.045 moles) in demineralized water (50 ml) and acetone (100 ml) at 5-10°C. The temperature was slowly raised to 15-20°C and the reaction mass was stirred at 15-20°C for 4 hours when the HPLC indicated the reaction to be complete. The mixture was filtered, pH was adjusted to 1.5 – 2.5 with the slow addition of 0.1N hydrochloric acid and the reaction mass was stirred for 10 hours at 15-20°C. The precipitated solid was filtered under vacuum, successively slurry washed with demineralized water (5 x 50 ml), suck dried for 1 hour and then dried at 45-50°C under vacuum till the moisture content was below 0.5% to afford 8.92 g of nateglinide form H as a white crystalline solid having purity 99.78% by HPLC (Yield = 93.89 %).

Method 11: Nateglinide methyl ester (10.0 g, 0.03 moles) was added to a solution of sodium hydroxide (1.81 g, 0.045 moles) in demineralized water (90 ml) and acetone (100 ml) at 5 to 10°C. The temperature was slowly raised to 15-20°C and reaction mass was stirred at 15-20°C for 4 hours when the HPLC indicated the reaction to be complete. The mixture was filtered to

remove suspended particles, pH was adjusted to 1.5 – 2.5 with slow addition of 1N hydrochloric acid. The reaction mass was stirred for 10 hours at 15-20°C and the precipitated solid was filtered under vacuum, successively slurry washed with demineralized water (5 x 50 ml), (till the filtrate indicated the absence of chloride ion), suck dried for 1 hour and then dried at 45-50°C under vacuum till the moisture content was below 0.5% to afford 8.7 g of nateglinide as a white crystalline solid having purity 99.74% by HPLC (Yield = 92.31 %).

Example 8: Preparation of Nateglinide form H

Nateglinide (10.0 g,) was dissolved in tetrahydrofuran (25 ml), acetonitrile (12.5 ml) was the added and the mixture was stirred at 25-30°C for 5 minutes. Demineralized water (300 ml) was slowly added to the solution and the mixture was stirred for 6 hours at 25-30°C. The precipitated solid was filtered, washed with water (3 x100 ml) and dried at 45-60°C to afford 8.0 g of nateglinide form H having purity of 99.67% by HPLC.

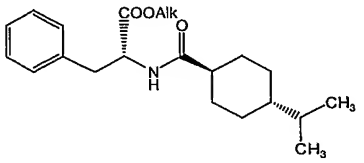
Example 9: Preparation of Nateglinide form H

Nateglinide (10.0 g, polymorphic form B) was dissolved in a mixture of tetrahydrofuran (25 ml) and methanol (25 ml) and the mixture was stirred at 25-30°C for 5 minutes. Demineralized water (300 ml) was slowly added to the solution and the mixture was stirred for 6 hours at 25-30°C. The precipitated solid was filtered, washed with demineralized water (3 x100 ml) and dried at 45-60°C to afford 8.44 g of nateglinide form H.

WE CLAIM

1. A process for the preparation of highly pure nateglinide form B which comprises:

hydrolysing *N*-(trans-4-isopropylcyclohexyl) carbonyl]-*D*-phenylalanine alkyl ester of formula II,



Formula II

wherein Alk is C_1-C_4 alkyl

with alkali metal hydroxide in a mixture of water and a suitable solvent at 0-35°C, preferably at 10-30°C,

optionally filtering the solution to remove the suspended particles,

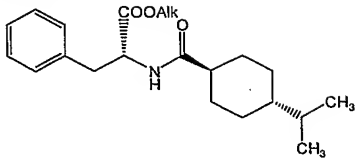
cooling the reaction mass to 5-15°C,

treating the reaction mass with dilute mineral acid till the pH of the solution is 1.5- 2.5,

and isolating highly pure nateglinide form B.

2. The process according to claim 1, wherein the alkyl ester is preferably methyl ester and ethyl ester.
3. The process according to claim 1, wherein the suitable solvent is selected from water miscible solvents like ethers, alcohols, nitriles, the like or mixtures thereof.
4. The process according to claim 1, wherein solvent is selected from tetrahydrofuran, methanol or acetonitrile or mixtures thereof.
5. The process according to claim 1, wherein the mineral acid used is hydrochloric acid.
6. A process for the preparation of nateglinide form B comprising crystallizing nateglinide in any polymorphic form other than B-type crystals, from suitable solvent such as ether, evaporating the solvent and isolating nateglinide form B.
7. The process according to claim 6, wherein ethereal solvent is selected from tetrahydrofuran, dimethyl ether, diethyl ether and the like.
8. A process for the preparation of nateglinide form B comprising dissolving nateglinide in a solvent selected from alcohols, nitriles or ethers, cooling the reaction mass, adding an anti-solvent such as water to precipitate nateglinide form B, and isolating nateglinide form B.
9. A process for the preparation of highly pure nateglinide form H which comprises:

hydrolyzing *N*-(trans-4-isopropylcyclohexyl)carbonyl]-*D*-phenylalanine alkyl ester of formula II,



Formula II

wherein Alk is straight or branched chain C_1-C_4 alkyl,

with base in a solution of suitable solvent like ether or ketone along with water at a temperature of 5-35°C;

optionally adding demineralized water to the reaction mixture;

treating the reaction mass with mineral acid to adjust pH of 1.0- 3.0, at a temperature of 15-60°C and;

isolating highly pure nateglinide Form H.

10. The process according to claim 9, wherein the alkyl ester is preferably methyl ester or ethyl ester.

11. The process according to claim 9, wherein the suitable ethereal solvent is selected from tetrahydrofuran, 1,4-diethoxy tetrahydrofuran, 1,4-dimethoxy tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxy ethane, 1,2-diethoxy ethane, the like and mixtures thereof.

12. The process according to claim 9, wherein the suitable ethereal solvent is tetrahydrofuran.

13. The process according to claim 9, wherein the suitable ketonic solvent is selected from C_3-C_{10} ketones, more preferably aliphatic ketones like acetone, diethyl ketone, ethyl methyl ketone, diisopropyl ketone, methyl propyl ketone, methyl isobutyl ketone, the like and mixtures thereof.

14. The process according to claim 9, wherein the suitable ketonic solvent is acetone.

15. The process according to claim 9, wherein the base is selected from alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide; alkaline metal carbonate such as potassium carbonate, sodium carbonate, , the like or a mixture thereof.

16. The process according to claim 9, wherein the base is sodium hydroxide.

17. The process according to claim 9, wherein the mineral acid used is preferably hydrochloric acid.

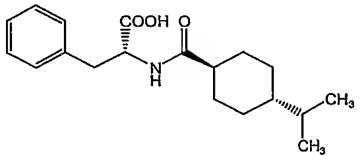
18. The process according to claim 9, wherein when the solvent is ethereal solvent such as tetrahydrofuran, the reaction mass is stirred at 20-30°C after the addition of mineral acid.

19. The process according to claim 9, wherein additional demineralized water is added before the addition of hydrochloric acid.

20. The process according to claim 9, wherein additional demineralized water is added after the addition of hydrochloric acid.

21. The process according to claim 9, wherein additional demineralized water is added in mixture with hydrochloric acid.

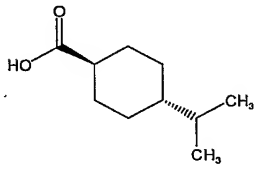
22. A process for the preparation of nateglinide of formula-I,



Formula I

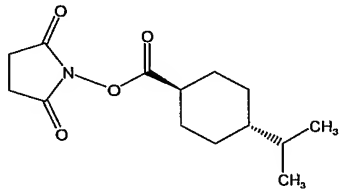
comprising:

a) reacting trans-4-isopropylcyclohexyl-1-carboxylic acid of formula III,



Formula III

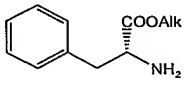
with *N*-hydroxysuccinimide in the presence of an organic base and *N,N*-dicyclohexylcarbodiimide in a halogenated solvent to form crude trans-4-isopropyl cyclohexylcarboxylate-*N*-hydroxysuccinimide ester of Formula IV,



Formula IV

b) purifying crude ester of Formula IV from a suitable organic solvent,

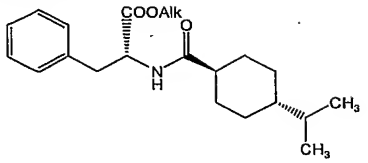
c) reacting trans-4-isopropylcyclohexylcarboxylate-*N*-hydroxysuccinimide ester of formula IV with *D*-phenylalanine alkyl ester of formula V,



Formula V

wherein Alk is C_1-C_4 alkyl

in a halogenated solvent such as dichloromethane in the presence of a base to form *N*-(trans-4-isopropylcyclohexyl) carbonyl]-*D*-phenylalanine alkyl ester of Formula II,



Formula II

wherein Alk is C_1-C_4 alkyl

d) purifying *N*-(trans-4-isopropylcyclohexyl) carbonyl]-*D*-phenylalanine alkyl ester of Formula II from a suitable organic solvent,

e) converting the same to nateglinide of Formula I.

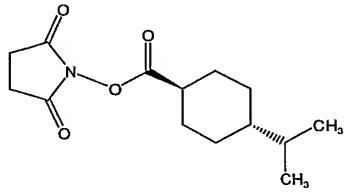
23. The process according to claim 22, wherein in step a, the organic base is selected from triethylamine, diisopropyl ethyl amine, triisopropyl amine, tributyl amine, pyridine or substituted pyridines.

24. The process according to claim 22, wherein in step b, the suitable organic solvent is selected from C_1-C_3 alcohols, esters formed by C_1-C_3 alcohols and C_1-C_3 acids, C_5-C_7 alkanes, ketones such as acetone, diethyl ketone, methyl isobutyl ketone or mixtures thereof.

25. The process according to claim 22, wherein in step c, the organic base is triethylamine.

26. The process according to claim 22, wherein in step d, the suitable organic solvent is selected from C_1-C_3 alcohols; ketones such as acetone, diethyl ketone, methyl isobutyl ketone; ethers such as tetrahydrofuran, 1,4-dimethoxy furan or alkyl ethers like diethyl ethers, diisopropyl ether, or a suitable mixture thereof.

27. A process for the purification of trans-4-isopropylcyclohexylcarboxylate-*N*-hydroxysuccinimide ester of formula IV,



Formula IV

which comprises:

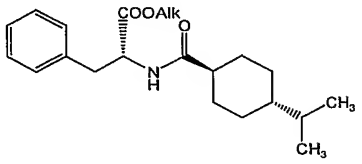
dissolving trans-4-isopropyl cyclohexylcarboxylate-*N*-hydroxysuccinimide ester of formula IV in a suitable organic solvent selected from C_1-C_3 alcohols, esters formed by C_1-C_3 alcohols and C_1-C_3 acids, C_5-C_7 alkanes, ketones such as acetone, diethyl ketone, methyl isobutyl ketone or mixture thereof,

heating the mixture with stirring at 50-75°C for a period of 1-4 hours,

cooling the mixture to a temperature of below 15°C,

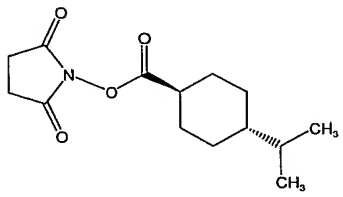
and isolating the pure trans-4-isopropylcyclohexylcarboxylate-*N*-hydroxysuccinimide ester of formula IV.

28. A process for the preparation of *N*-(trans-4-isopropylcyclohexyl)carbonyl]-*D*-phenylalanine alkyl ester of formula II,



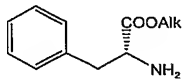
Formula II

which comprises reacting trans-4-isopropylcyclohexylcarboxylate-*N*-hydroxylsuccinimide ester of formula IV,



Formula IV

with *D*-phenylalanine alkyl ester of formula V ,



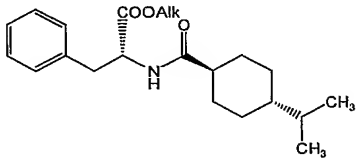
Formula V

wherein Alk is C_1-C_4 alkyl

in a halogenated solvent in the presence of a base to form *N*-(trans-4-isopropylcyclohexyl)carbonyl]-*D*-phenylalanine alkyl ester of Formula II.

29. The process according to claim 28, wherein the halogenated solvent is dichloromethane and the base is triethyl amine.

30. A process for the purification of *N*-(trans-4-isopropylcyclohexyl)carbonyl]-*D*-phenylalanine alkyl ester of formula II,



Formula II

wherein Alk is C_1-C_4 alkyl

which comprises:

a) dissolving *N*-(trans-4-isopropylcyclohexyl) carbonyl]-*D*-phenylalanine methyl ester of formula II in suitable organic solvent selected from C_1-C_3 alcohols; ketones such as

acetone, diethyl ketone, methyl isobutyl ketone; ethers such as tetrahydrofuran, 1,4-dimethoxy furan or alkyl ethers like diethyl ethers, diisopropyl ether, or a suitable mixture thereof,

b) cooling the mixture to a temperature of below 10°C,

c) and isolating the pure *N*-(trans-4-isopropylcyclohexyl)carbonyl]-*D*-phenylalanine methyl ester of formula II.

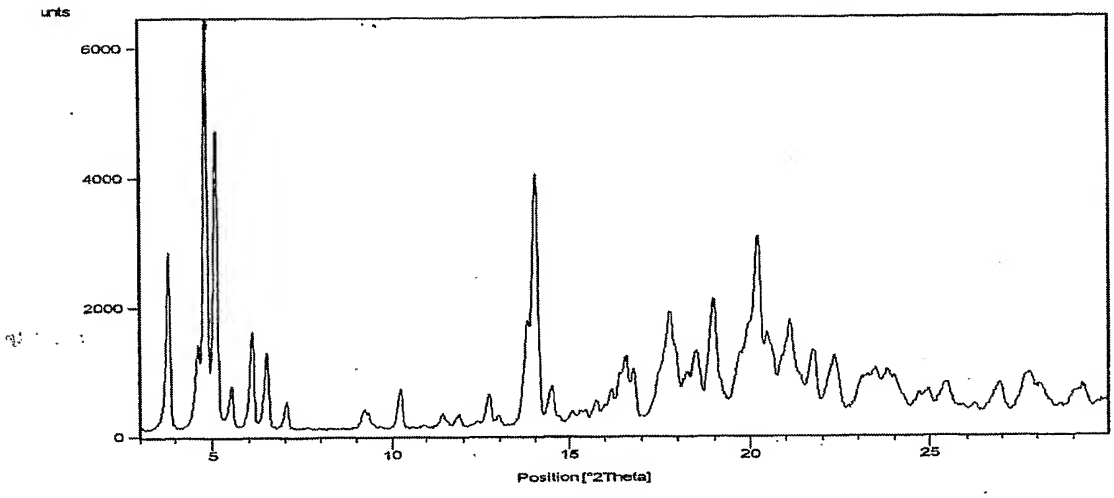


Figure 1

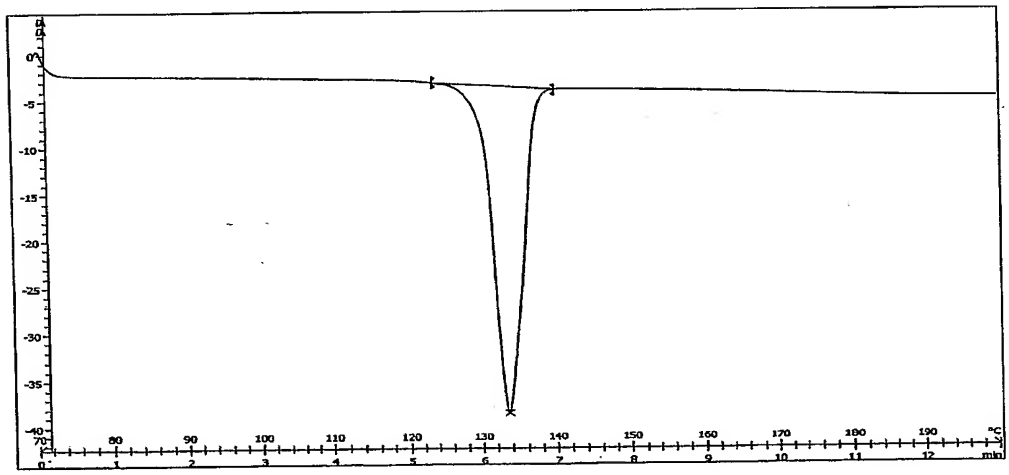


Figure 2

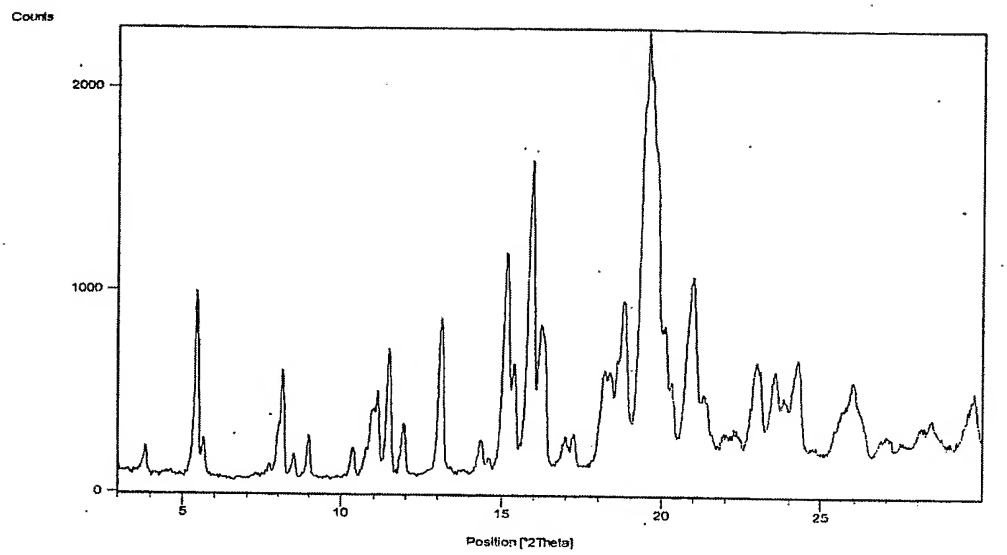


Figure 3

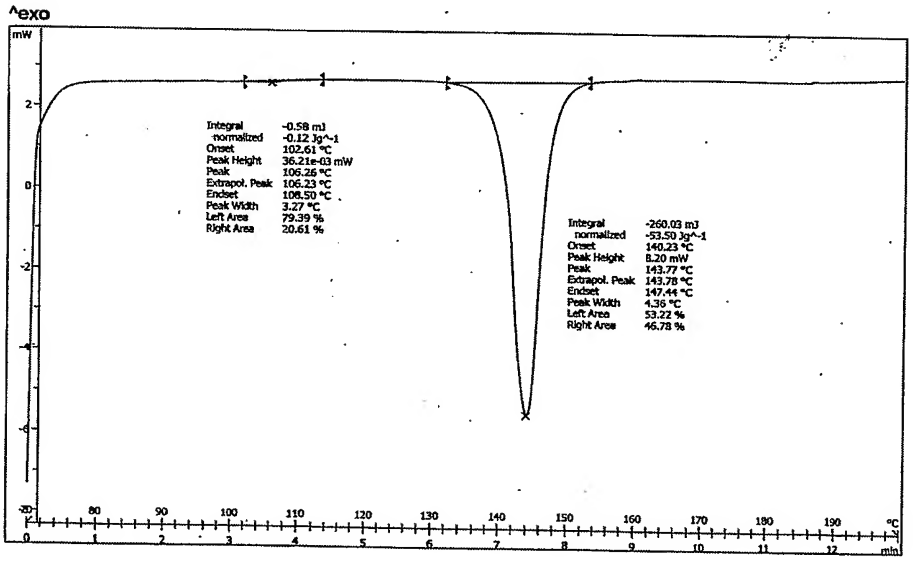


Figure 4